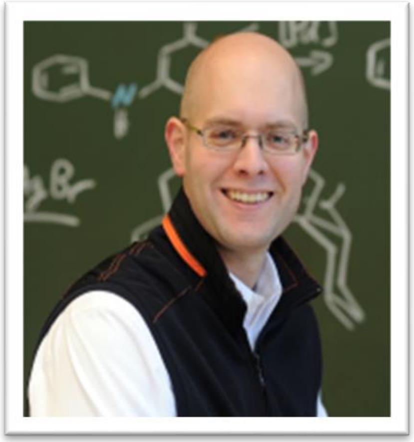
Literature Report VII

Silver-Enabled Cycloaddition of Bicyclobutanes with Isocyanides for the Synthesis of Polysubstituted 3-Azabicyclo[3.1.1]heptanes

Reporter: Shan-Shan Xun
Checker: Han Wang
Date: 2023-04-15

Liang, Y.; Nematswerani, R.; Daniliuc, C. G.; Glorius, F.*
Angew. Chem. Int. Ed. **2024**, e202402730

CV of Prof. Frank Glorius



Frank Glorius

Background:

- **1992-1997** Studies of chemistry, the University of Hannover
- **1995-1996** Research studies, Stanford University
- **1996-1997** Diploma thesis, University of Hannover
- **1997-2000** PhD, University of Basel
- **2000-2001** Postdoc., Harvard University
- **2001-2004** Independent research at the Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr
- **2004-2007** C3-Professor, University of Marburg
- **2007-now** Full Professor, University of Münster

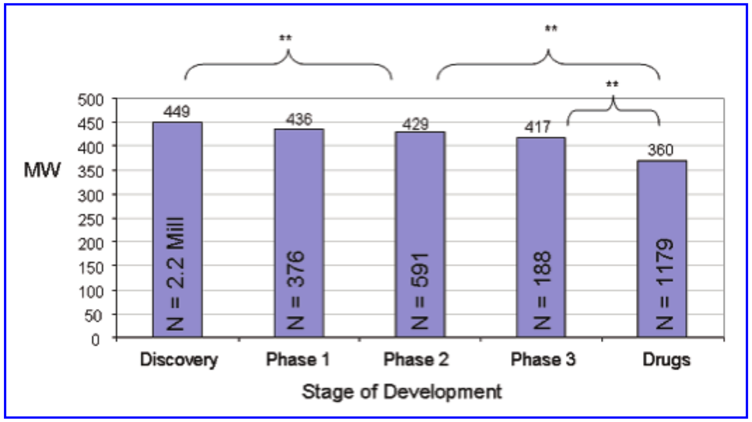
Research Interests:

- Arene Hydrogenation
- C-H Activation
- Photocatalysis
- *N*-Heterocyclic Carbene (NHC) Organocatalysis

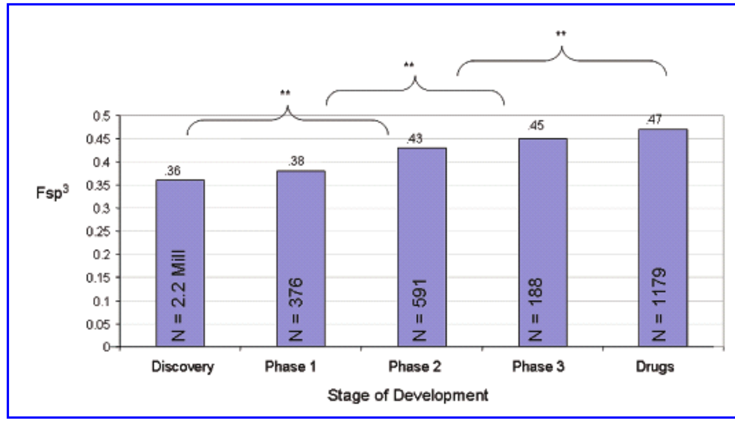
Contents

Introduction

Escape from Flatland Concept: Increasing Saturation as an Approach to Improving Clinical Success



Mean molecular weight for compounds in different stages of development



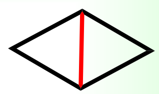
Mean Fsp^3 for compounds in different stages of development

- Increasing sp^3 character may enhance molecular properties for clinical success
- Reducing a molecule's aromatic character can enhance solubility, especially for intravenous compounds
- Compounds with higher saturation are more likely to succeed in every stage from discovery to drug development

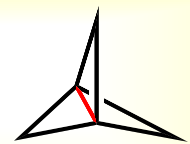
Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752

Introduction

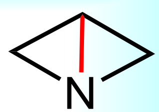
Spring-loaded



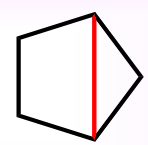
双环[1,1,0]丁烷（BCB)
bicyclo[1.1.0]butane



[1.1.1]螺桨烷（TCP)
[1.1.1]propellane

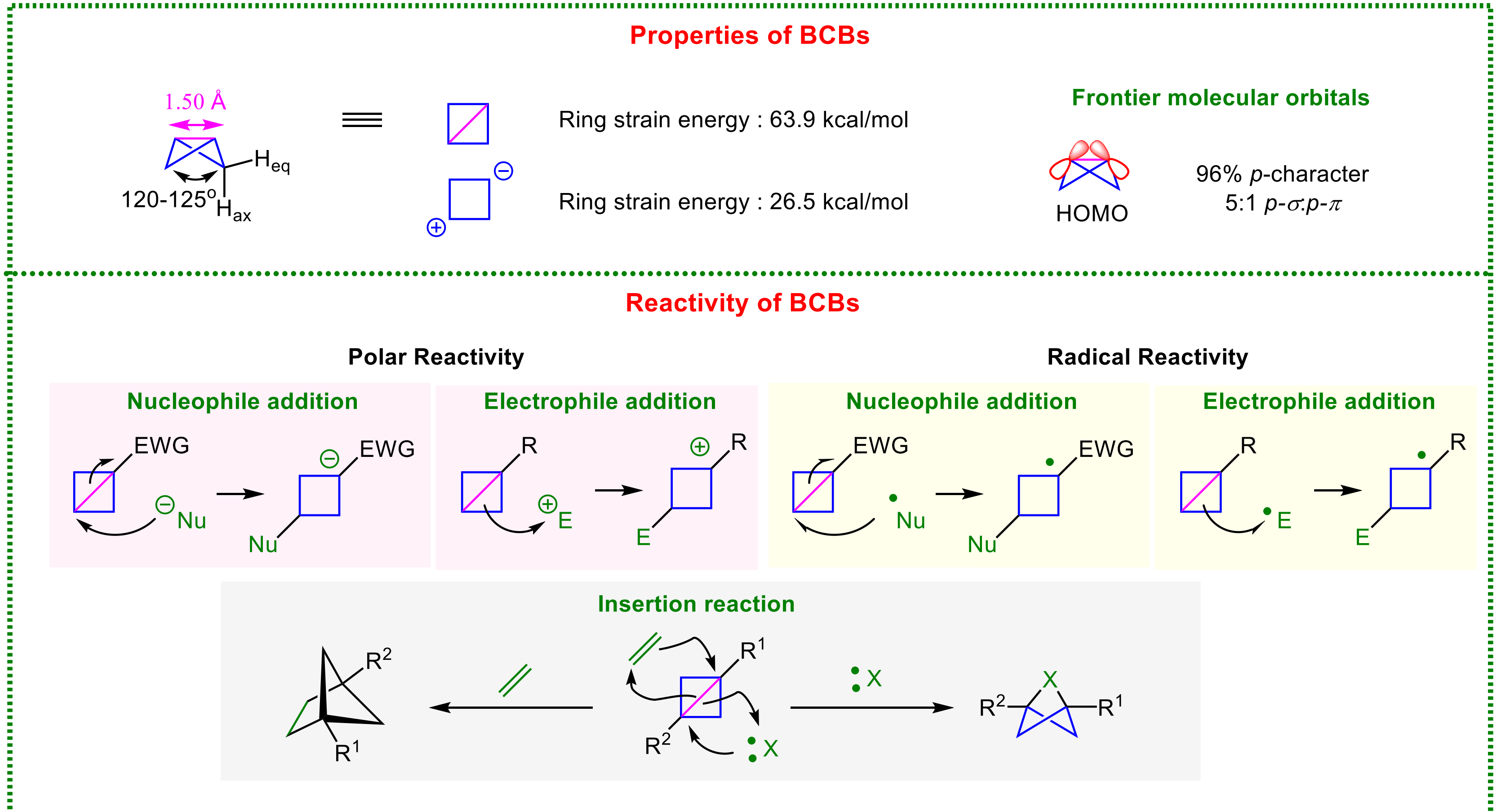


氮杂双环[1,1,0]丁烷（ABB)
azabicyclo[1.1.0]butane



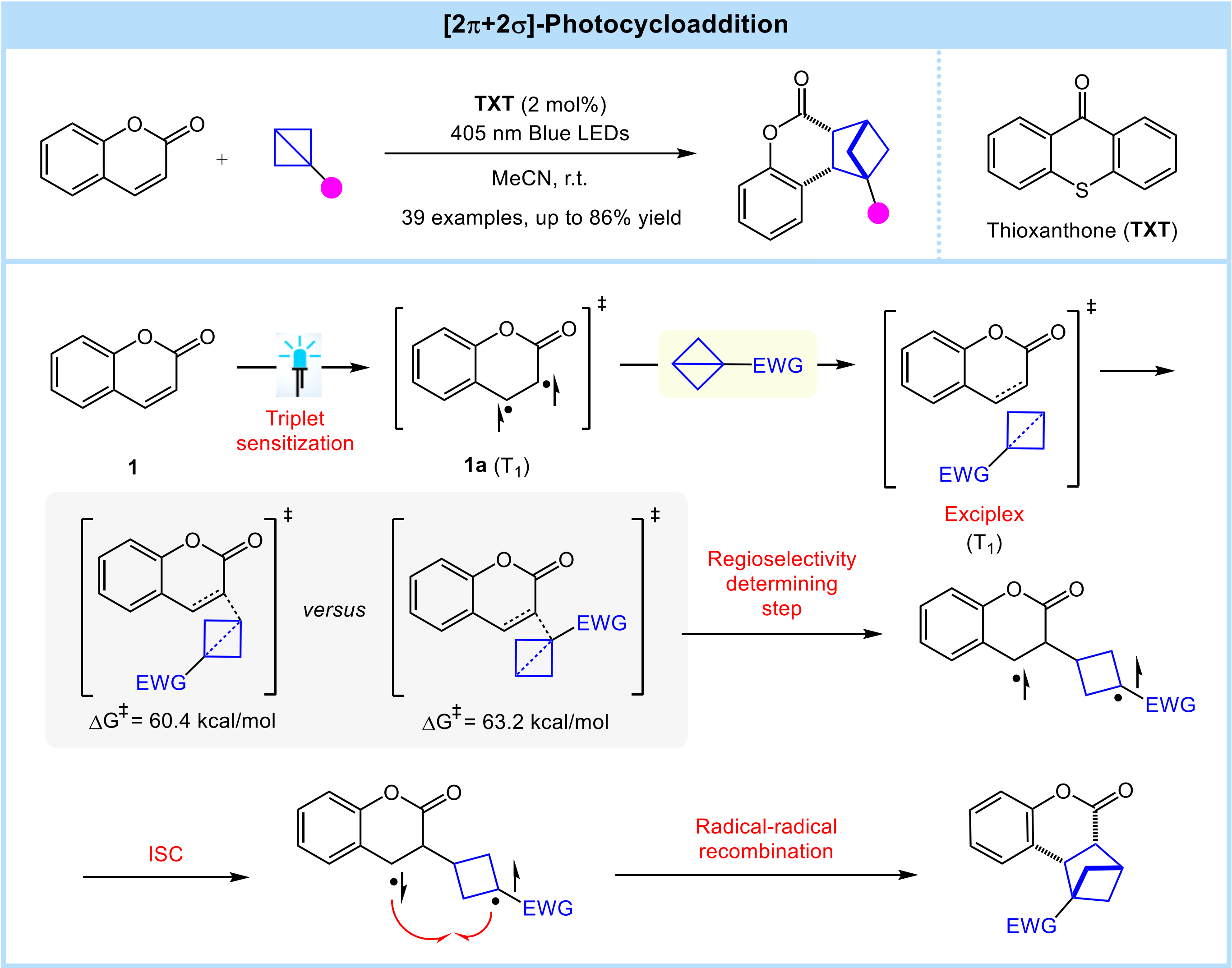
双环[2.1.0]戊烷（Housane)
bicyclo[2.1.0]pentane

Introduction



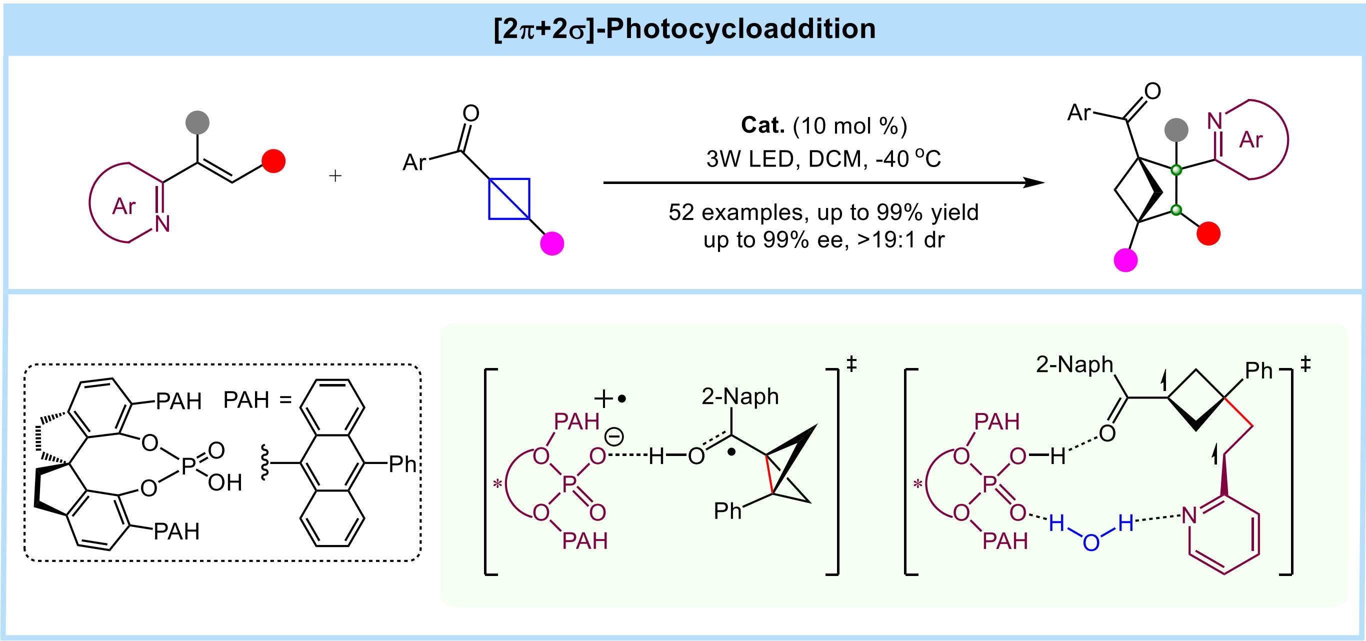
Golfmann, M.; Walker, J. C. L. *Commun. Chem.* **2023**, *6*, 9

Introduction



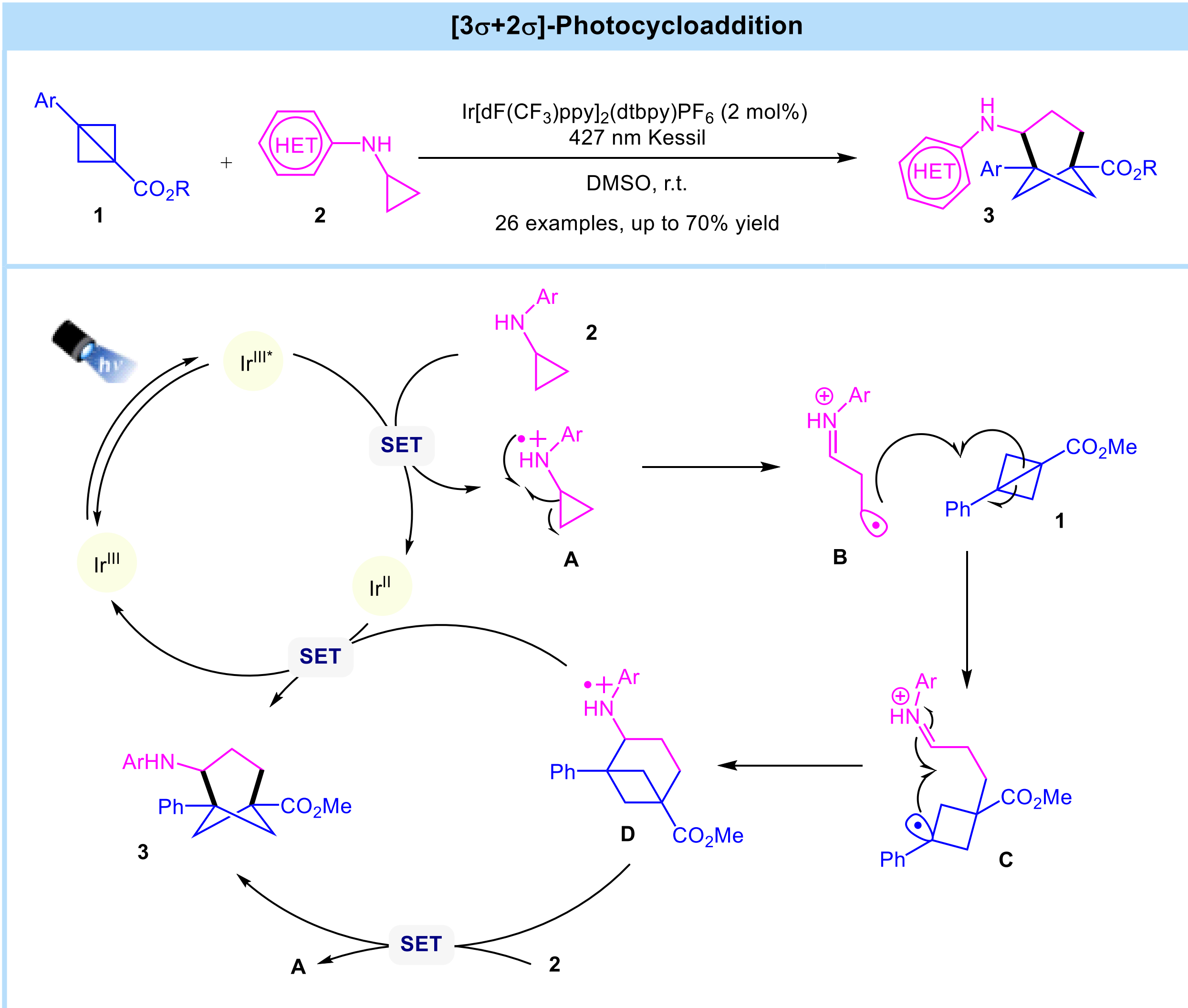
Kleinmans, R.; Dutta, S.; Paulisch, T. O.; Keum, H.; Daniliuc, C. G.; Glorius, F. *Nature* **2022**, *605*, 477

Introduction



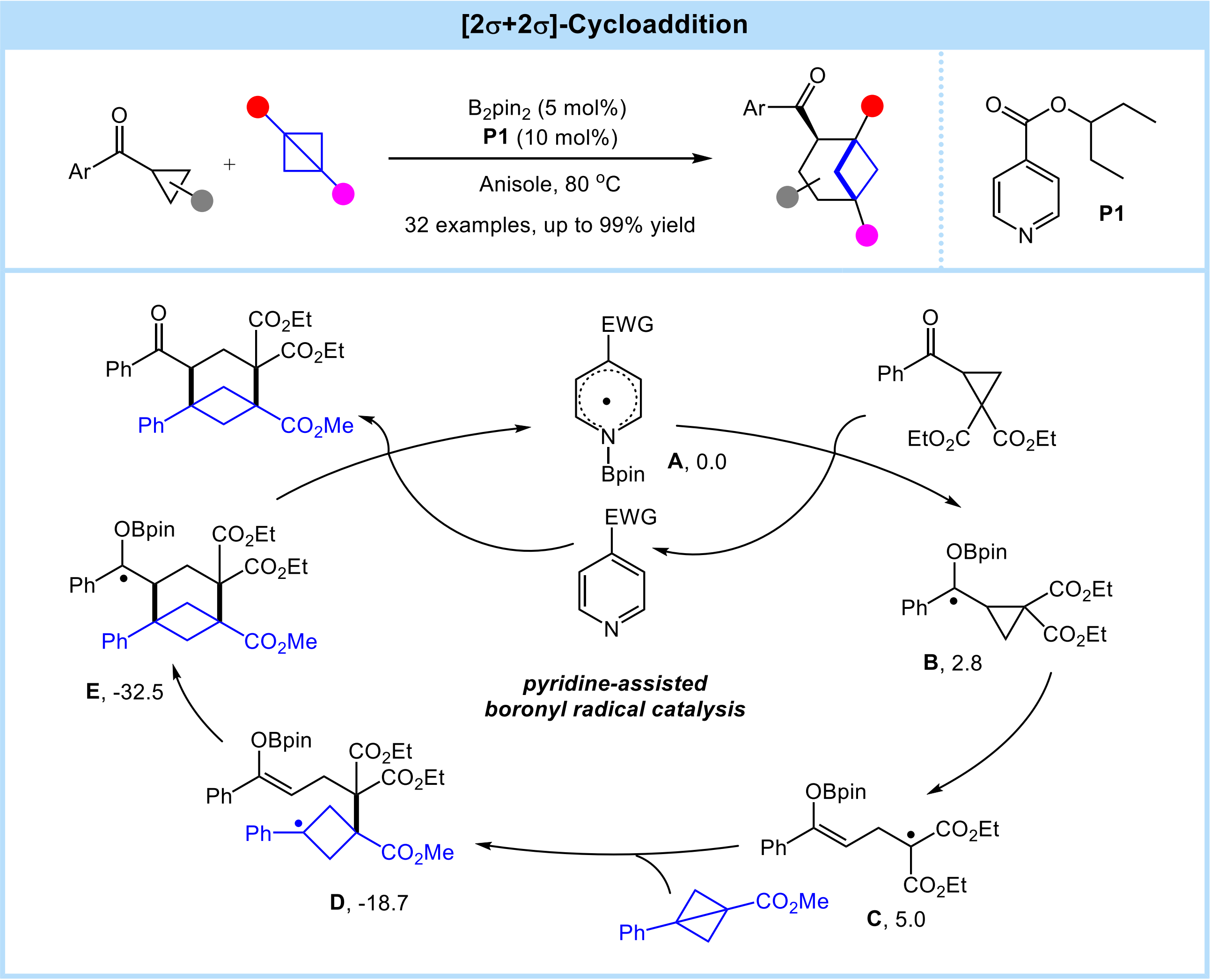
Fu, Q.; Cao, S.; Wang, J.; Lv, X.; Wang, H.; Jiang, Z. *J. Am. Chem. Soc.* **2024**, *146*, 8372

Introduction



Zheng, Y.; Makvandi, M.; Molander, G. A. *J. Am. Chem. Soc.* **2022**, *144*, 23685

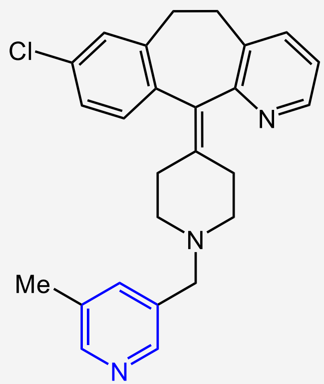
Introduction



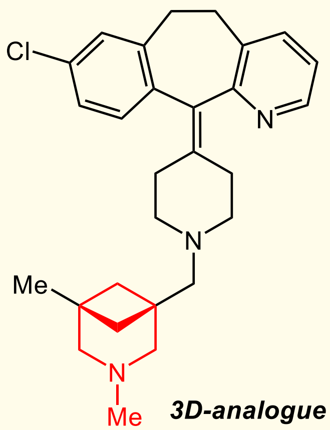
Yu, T.; Yang, J.; Wang, Z.; Ding, Z.; Xu, M.; Li, P. *J. Am. Chem. Soc.* **2023**, *145*, 4304

Introduction

Saturated Analogue of A Drug



Antinistomine drug
Rupatadine

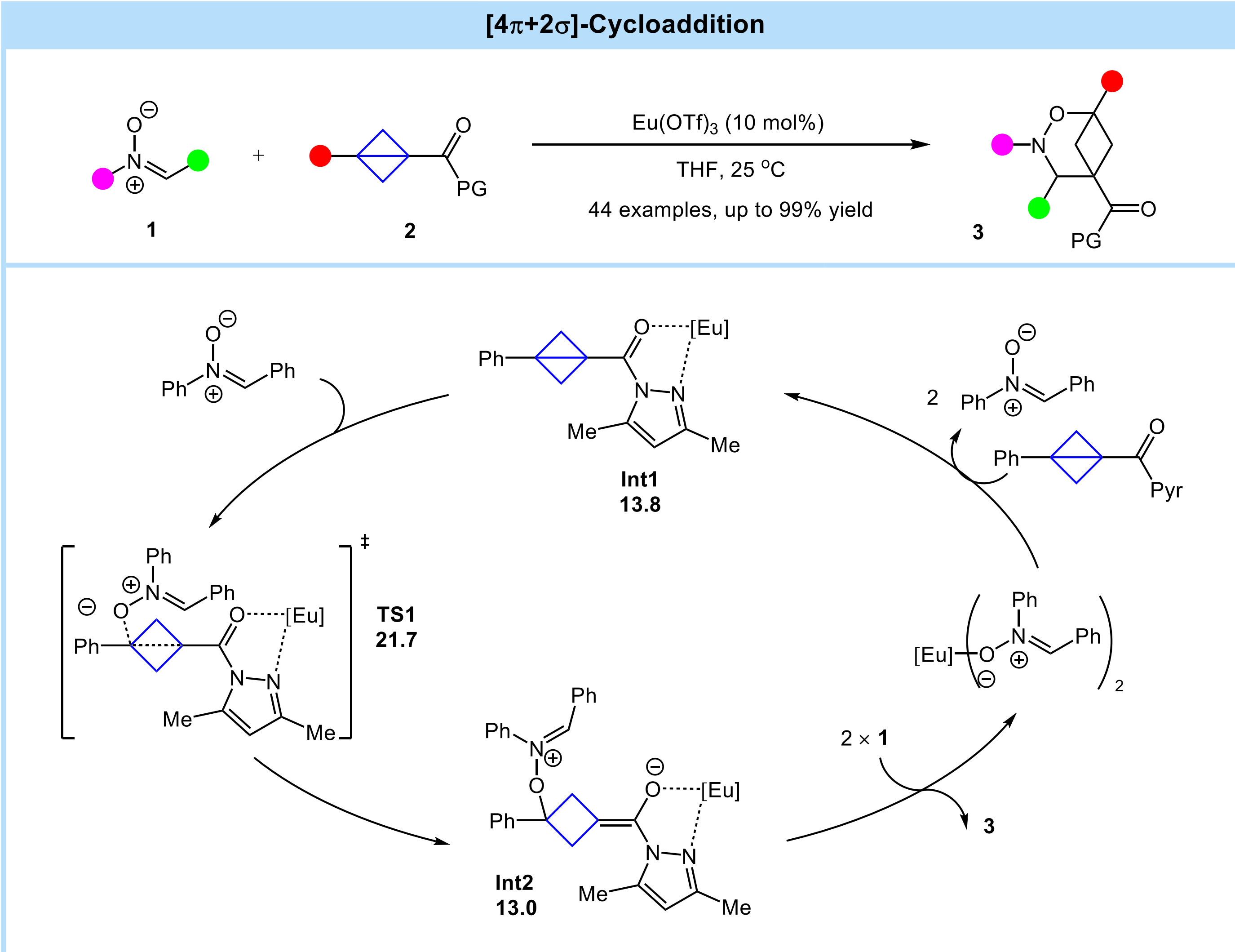


3D-analogue
Rupatadine

Compound	*Sol.* (μM)	*clogP*	*logD (7.4)*	CL_{int} ($\mu L min^{-1} mg^{-1}$)	$t_{1/2}$ (min)
Rupatadine	29	5.1	>4.5	517	3.2
3D-analogue **Rupatadine**	365	5.2	3.8	47	35.7

Dibchak, D.; Snisarenko, M.; Mykhailiuk, P. K. *Angew. Chem. Int. Ed*. **2023**, *62*, e202304246

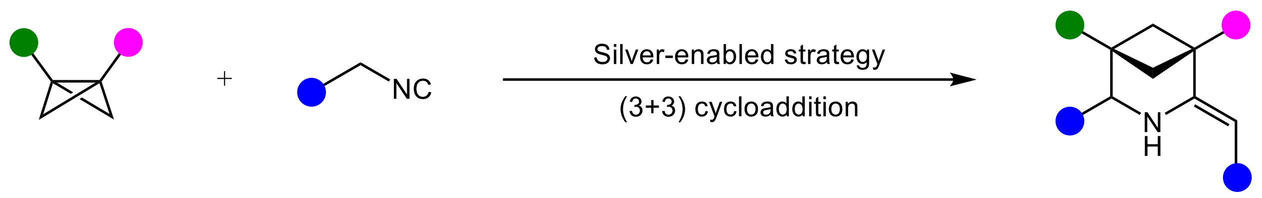
Introduction



Zhang, J.; Su, J.-Y.; Zheng, H.; Li, H.; Deng, W.-P. *Angew. Chem. Int. Ed.* **2024**, *63*, e202318476

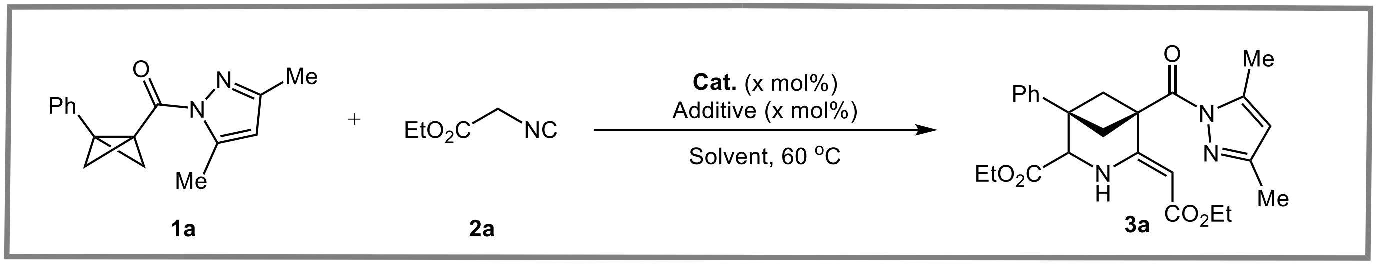
Project Synopsis

Silver-Enabled (3+3) Cycloaddition of BCBs



- Exhibit incredible potential as pyridine bioisoster
- Enrich the growing set of valuable sp^3-rich bicyclic building blocks
- The direct (3+3) cycloaddition of BCBs represents a highly attractive way

Optimization of Reaction



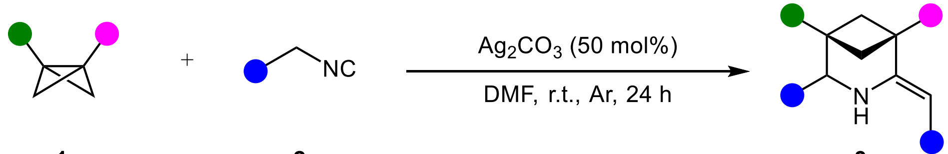
Entry[a]	Cat. (mol%)	2a (equiv.)	Solvent	Yield[a]
1	AgOTf (10)	3	MeCN	--
2	$AgNO_3$ (10)	3	MeCN	--
3	AgOAc (10)	3	MeCN	<5
4	Ag_2CO_3 (10)	3	MeCN	16
5	Li_2CO_3 (10)	3	MeCN	--
6	K_2CO_3 (10)	3	MeCN	--
7	$CuCO_3{\cdot}Cu(OH)_2$ (10)	3	MeCN	--
8	$NiCO_3$ (10)	3	MeCN	--
9	Ag_2CO_3 (20)	3	MeCN	24
10	Ag_2CO_3 (20)	10	MeCN	33
11	Ag_2CO_3 (30)	10	MeCN	49
12	Ag_2CO_3 (40)	10	MeCN	60
13	Ag_2CO_3 (50)	10	MeCN	62

Optimization of Reaction

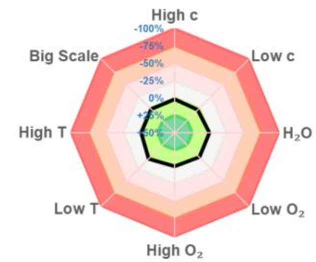
Entry[a]	Cat. (mol%)	2a (equiv.)	Additive (mol%)	Solvent	Yield[a]
14	Ag_2CO_3 (10)	10	Li_2CO_3 (50)	MeCN	15
15	Ag_2CO_3 (10)	10	K_2CO_3 (50)	MeCN	21
16	Ag_2CO_3 (50)	8	--	MeCN	54
17	Ag_2CO_3 (50)	6	--	MeCN	50
18	Ag_2CO_3 (50)	10	--	THF	39
19	Ag_2CO_3 (50)	10	--	PhMe	33
20	Ag_2CO_3 (50)	10	--	DCE	37
21	Ag_2CO_3 (50)	10	--	DMF	79
22[b]	Ag_2CO_3 (50)	10	--	DMF	79
23[c]	Ag_2CO_3 (50)	10	--	DMF	78
24[c]	Ag_2CO_3 (100)	10	--	DMF	75
25[c]	--	10	--	DMF	--
26[d]	Ag_2CO_3 (50)	10	--	DMF	76

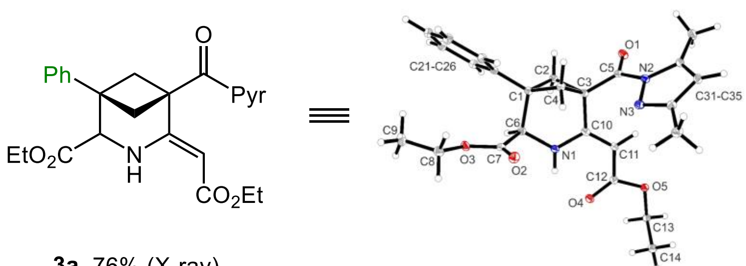
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst (10-100 mol%), solvent (1.0 mL), Ar, 60 ^{o}C, 24 h. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [b] Reaction conducted at 80 ^{o}C. [c] Reaction conducted at room temperature. [d] Reaction conditions: **1a** (0.2 mmol), **2a** (2 mmol), Ag_2CO_3 (50 mol%), DMF (2 mL), Ar, r.t., 24 h. Isolated yield is showed.

Substrate Scope

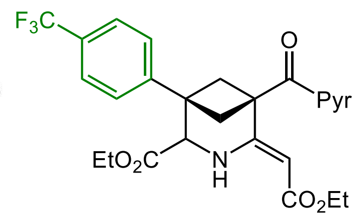


1 **2** **3**

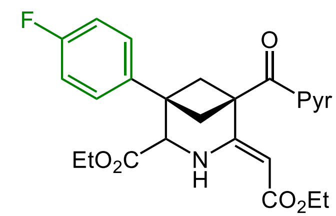




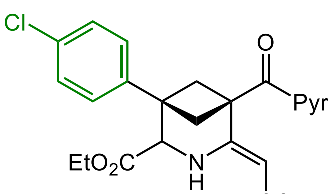
3a, 76% (X-ray)



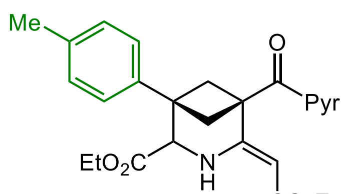
3b, 81%



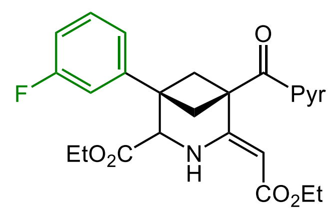
3c, 77%



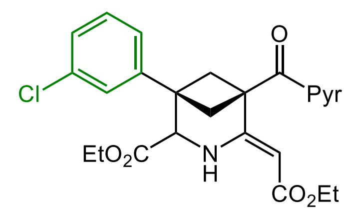
3d, 60%



3e, 71%

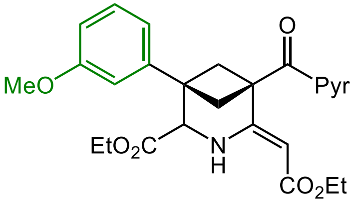


3f, 71%

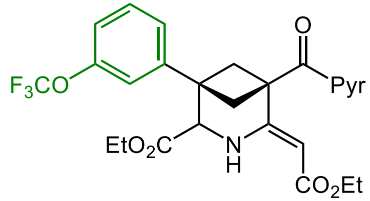


3g, 85%

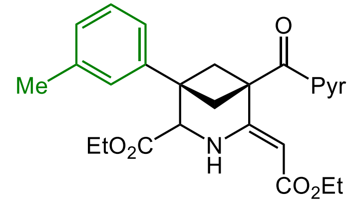
Substrate Scope



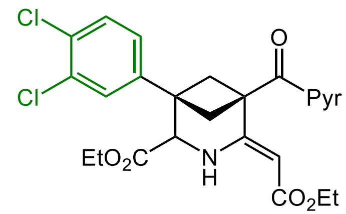
3h, 59% (X-ray)



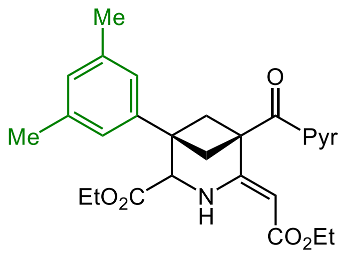
3i, 56%



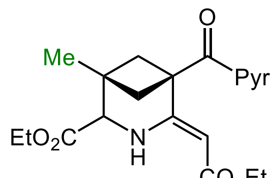
3j, 69%



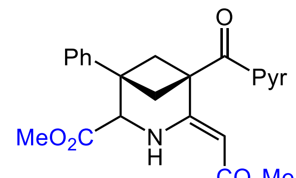
3k, 61%



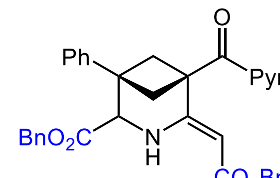
3l, 66%



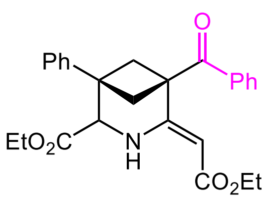
3m, 49%



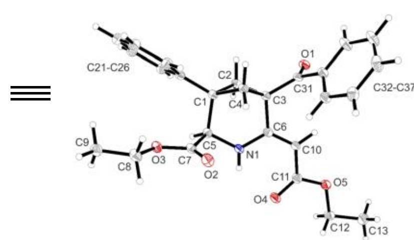
3n, 80%

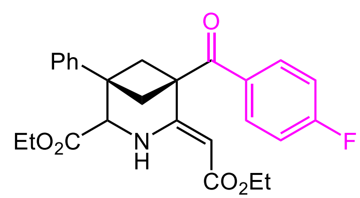


3o, 75%

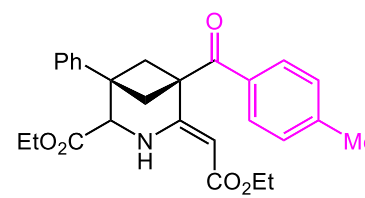


3p, 68% (X-ray)



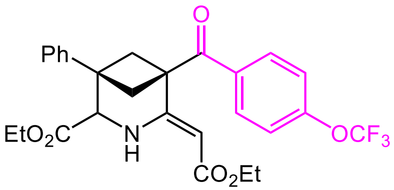


3q, 80%

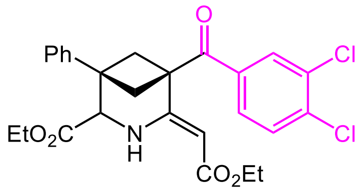


3r, 59%

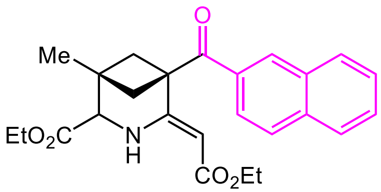
Substrate Scope



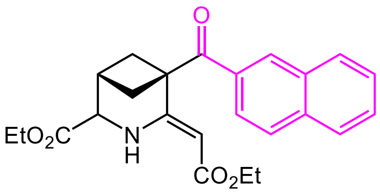
3s, 50%



3t, 47%

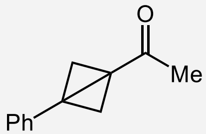


3u, 25%

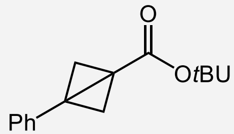


3v, 19%

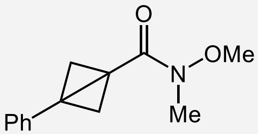
Unsuccessful substrates



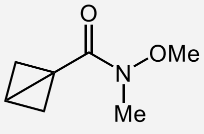
1n
trace



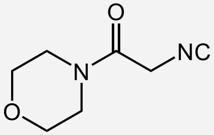
1o
n.d.



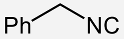
1w
n.d.



1x
n.d.

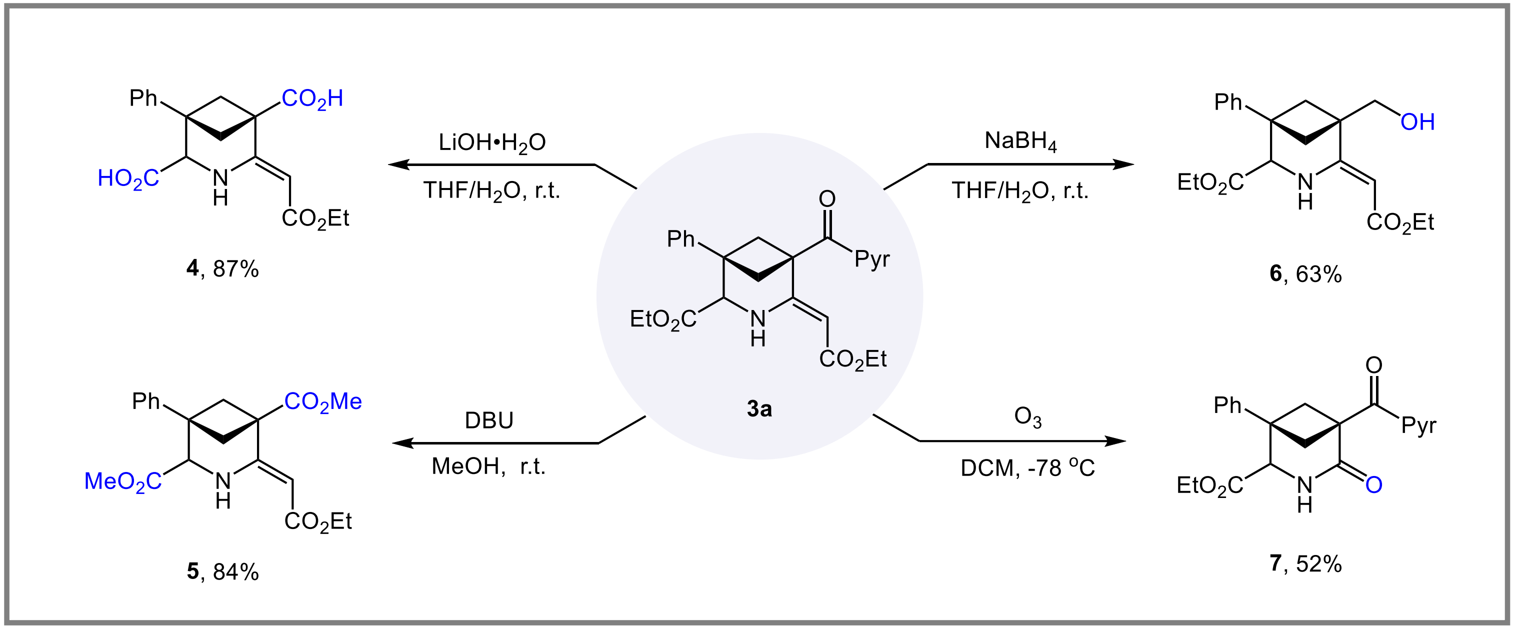


2d
n.d.



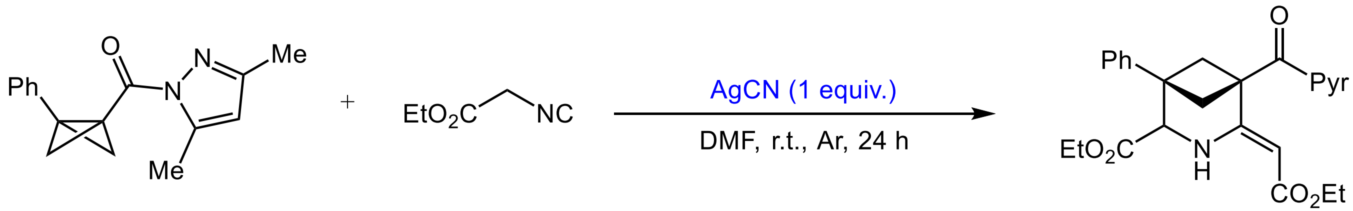
2e
n.d.

Synthetic Application



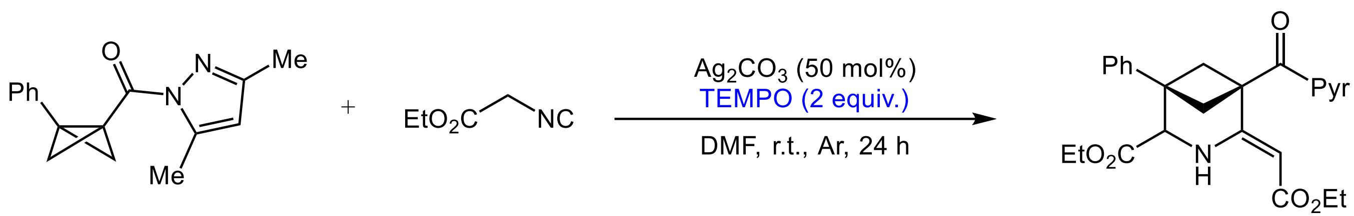
Mechanistic Studies

(a)



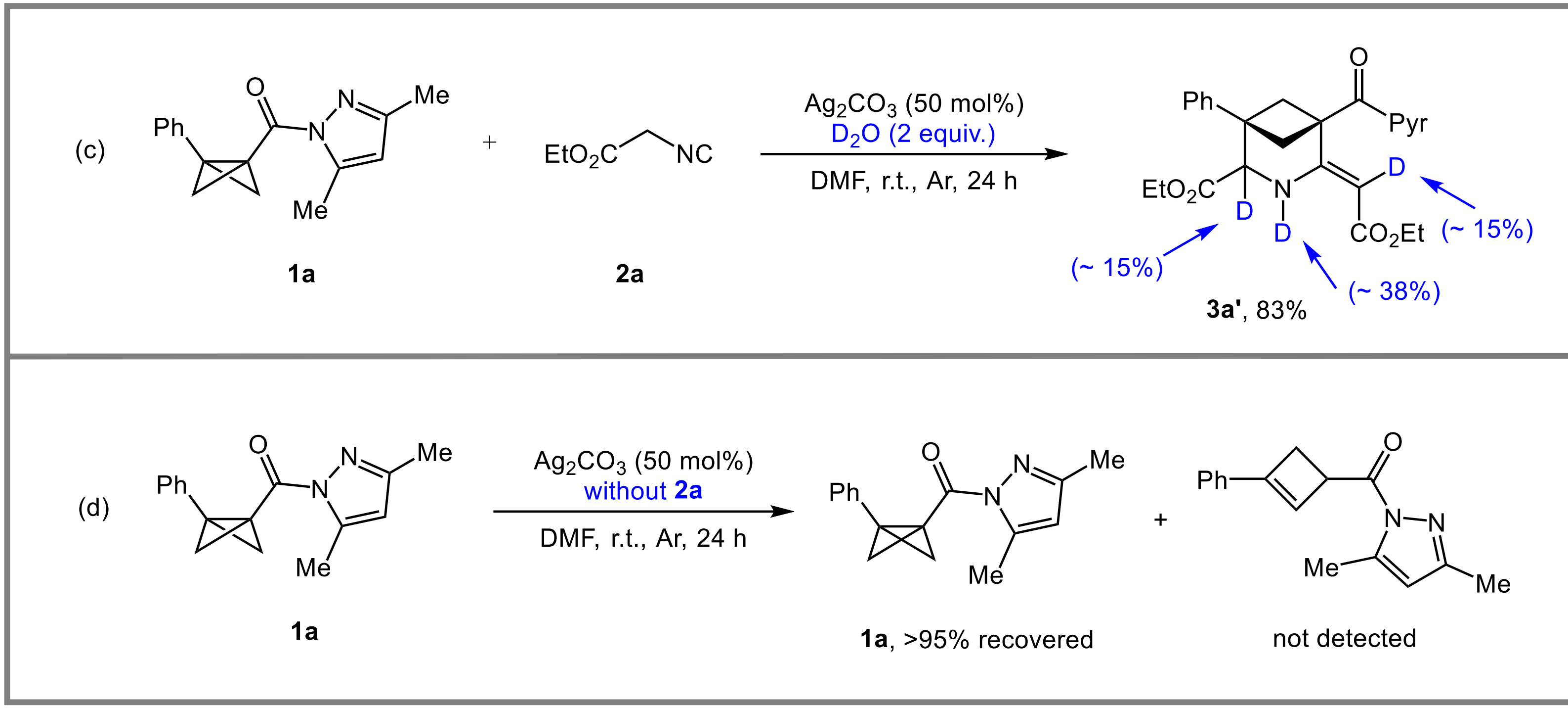
1a **2a** **3a**, not detected

(b)

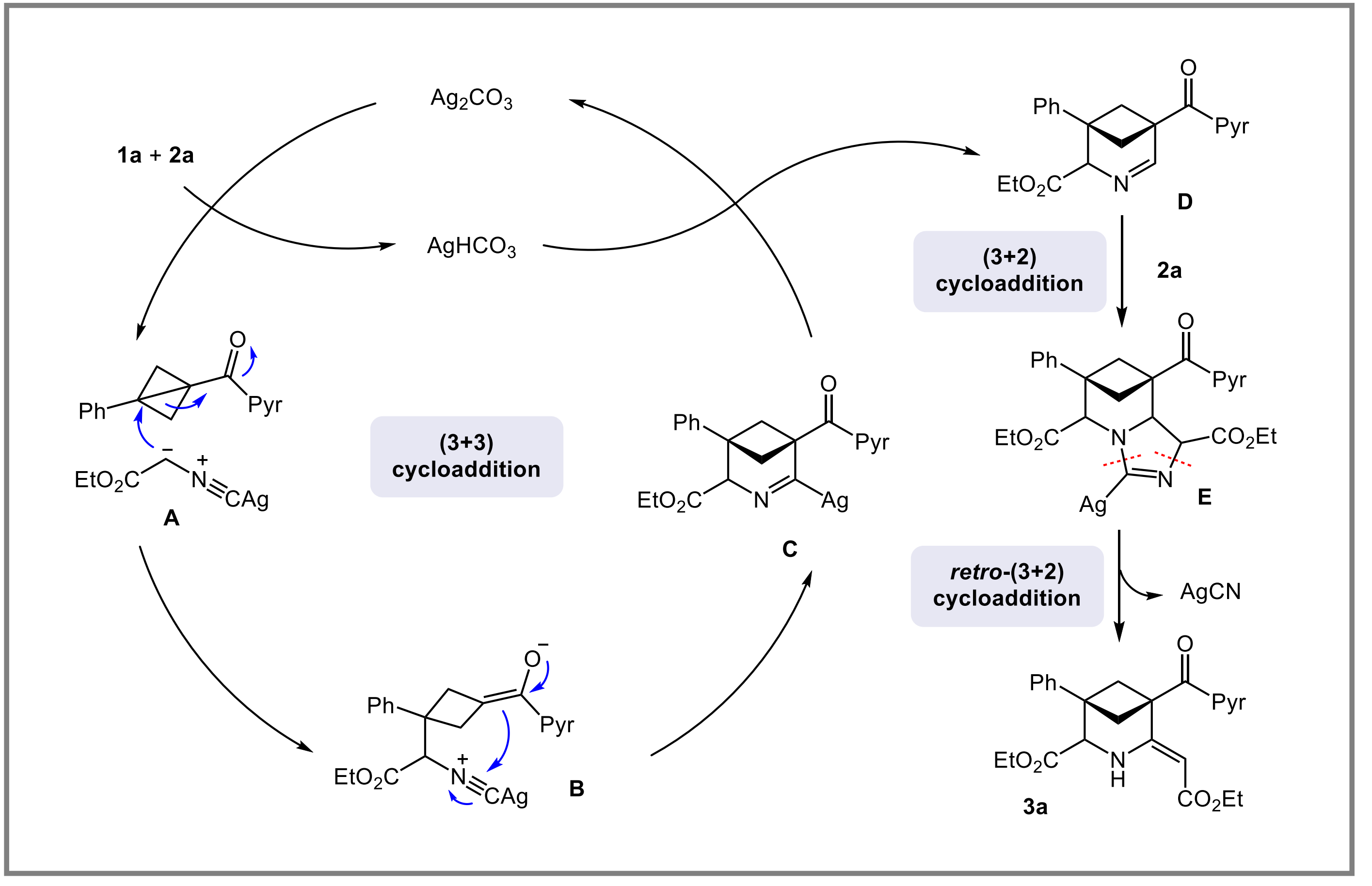


1a **2a** **3a**, 75%

Mechanistic Studies

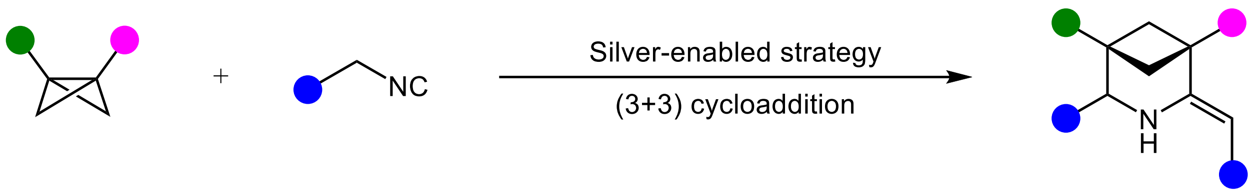


Proposed Mechanism



Summary

Silver-Enabled (3+3) Cycloaddition of BCBs



- 22 Examples, up to 85% yield
- Trigger a challenging (3+3) cycloaddition
- Direct construction of bicyclic building blocks
- Diverse array of downstream transformations

Writing Strategy

☐ The First Paragraph

"Escape from flatland" concept

↓

Importance of sp^3-hybridized carbon atom in drug candidates

↓

Significance

- ✓ Under the "escape from flatland" concept, saturated bicyclic scaffolds, due to their potential phenyl or pyridinyl bioisosterism, have witnessed a surgent growth of application in the field medicinal chemistry over the past decade.
- ✓ The bioisosteric replacement of aromatic rings with these conformationally rigid units intro-duces a higher proportion of sp^3-hybridized carbon atom into molecules, which is increa-seingly recognized as a powerful tool in modulat-ing the physicochemical and pharmacokinetic properties of drug candidates.
- ✓ Therefore, there is a growing interest of chem-ists in the development of efficient methods for the construction of these coveted ring systems

Writing Strategy

☐ The Last Paragraph

Summary
of this work

↓

Outlook
of this work

- ✓ **In conclusion, a practical silver-enabled cyclo-addition of BCBs with isocyanides has been developed, allowing for the direct construction of polysubstituted 3-*aza*-BCHeps which are demanding … A diverse array of downstream transformations of the resulted product have also been achieved, further demonstrating the synthetic utilities of this method.**

- ✓ **In contrast with the vast majority of (3+2) cyclo-addition of BCBs with π-components, this work provides new logics to trigger … novel cyclo-addition process, good functional group tolerance, and robustness of this protocol, the results of this work will likely be rapidly embraced by both pharmaceutical and academic laboratories.**

Representative Examples

The direct (3+3) cycloaddition of BCBs with a readily available *N*-component would represent a highly attractive way for their manufacture, but remains hitherto elusive. (难以理解的，难以捉摸的)

The different electrophilicity of the carbonyl groups in **7** offers opportunities for subsequent stepwise modification of the structure. (楼梯式的，逐步的)

Delightedly, the reaction of BCBs with a range of different substituents at the aryl moieties, including both electron-withdrawing and electron-donating groups. (高兴地，愉快地)

Thanks

for your attention